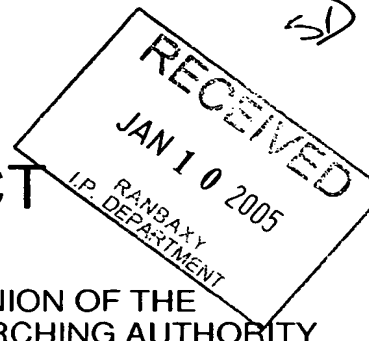


INTERNATIONAL COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2004/002040

International filing date (day/month/year)
18.06.2004

Priority date (day/month/year)
19.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07D501/00, A61K31/545

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/IB2004/002040

IAP20 Rec'd PCT/PTO 16 DEC 2005

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. II Priority

1. ☒ The following document has not been furnished:
- ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).
- Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
4. Additional observations, if necessary:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002040

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------------|
| Novelty (N) | Yes: Claims | 1, 4, 8, 9 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1, 4, 8, 9 |
| Industrial applicability (IA) | Yes: Claims | 1, 4, 8, 9 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

PCT/IB2004/002040

IAP20 Rec'd PCT/PTO 16 DEC 2005

Re Item IV.

The separate inventions/groups of inventions are:

a) claims 1-3, 8, 10-32(part)

N-methylpyrrolidone solvate of cefprozil, process for its preparation and its use in the preparation of crystalline cefprozil

b) claims 4-7, 9, 10-32(part)

N,N-dimethylacetamide solvate of cefprozil, process for its preparation and its use in the preparation of crystalline cefprozil

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The present subject matter is directed towards the synthesis of N-methylpyrrolidone and N,N-dimethylacetamide solvates of cefprozil. For the purposes of unity of invention, Rule, 13.1 PCT stipulates that an international application must relate to one invention only or to a group of inventions so linked as to form a single general (inventive) concept. It appears that solvates of cefprozil are known (cf US4694079 and WO03011871). In view of the said prior art, the problem underlying the present application may have been the provision of further solvates of cefprozil. Compared with the prior art, divergent solutions to this problem could be defined as subject-matter of the claims of the present application, based on the choice of the solvate used. This could for example mean that the following different approaches would have been considered by the skilled person: 1) Provision of the N-methylpyrrolidone solvate of cefprozil; 2) Provision of the N,N-dimethylacetamide solvate of cefprozil. These two processes share the common feature of being cefprozil solvates. These cannot however be considered as being a special technical features within the meaning of Rule 13.1 PCT, since solvates of cefprozil are known from e.g. US4694079 and WO03011871. Consequently there is lack of unity within the meaning of rule 13 PCT and the different inventions, not belonging to a common inventive concept, have to be formulated as different subjects pursuant to Article 17(3) (a) PCT.

Re Item V.

The following documents are referred to in this communication:

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/002040

- D1 : US 4 520 022 A (HOSHI HIDEAKI ET AL) 28 May 1985 (1985-05-28)
D2 : US 4 694 079 A (CRAST JR LEONARD B) 15 September 1987 (1987-09-15)
D3 : WO 03/011871 A (GREIL JULIA ; BIOCHEMIE GMBH (AT); WOLF SIEGFRIED (AT); LUDESCHER JOHA) 13 February 2003 (2003-02-13)
D4 : WO 03/047590 A (PHOENIX SCIENT INC) 12 June 2003 (2003-06-12)

NOVELTY (Article 33(2) PCT)

The present N-methylpyrrolidone solvate (group of inventions a) and N,N-dimethylacetamide solvate (group of inventions b) of cefprozil establishes novelty over D1-D4.

INVENTIVE STEP (Article 33(3) PCT)

The present subject matter is directed towards the provision of N-methylpyrrolidone (group of inventions a) and N,N-dimethylacetamide (group of inventions b) solvate of cefprozil.

D2 is considered to be the closest prior art and discloses DMF solvate of cefprozil.

The present subject matter differs from D2 on account of the use of N-methylpyrrolidone or N,N-dimethylacetamide instead of DMF as cefprozil solvate. Solvates of cefprozil are also disclosed in D3.

The problem to be solve by both present group of inventions a and b is considered to be the provision of further solvates of cefprozil.

Once the problem of providing further solvates of cefprozil is posed, the choice of N-methylpyrrolidone and/or N,N-dimethylacetamide appears to be just one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. Thus, it appears that an inventive step could be acknowledged for the present subject matter only if unexpected properties were shown for *both* N-methylpyrrolidone *and* N,N-dimethylacetamide with respect to the structurally closest solvates from the prior art. In the absence of any empirical data (e.g. comparative tests) showing such

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INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/002040

unexpected properties, an inventive step cannot be acknowledged for the present subject matter.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.